Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

Applicants' representative respectfully thanks the Examiner for the interview, in which the outstanding rejections were discussed.

By the present amendment, claim 59 has been amended to recite that an anticancer agent is administered to a patient with cancer, the anticancer agent induces formation of AP sites in cancer cells, and the amount of a base excision repair (BER) inhibitor administered to the patient is effective to potentiate the cytotoxicity of the anticancer agent. Claim 59 was further amended to recite that the AP endonuclease inhibitor includes an amine group and binds to the AP site to prevent AP endonuclease-mediated cleavage of phosphodiester bonds. Support for this language can be found on pages 18 and 19 of the application.

Below is a discussion of the 35 U.S.C. §112, first paragraph rejection of claims 59, 60, 64, 75, 77 and 98, the 35 U.S.C. §112, first paragraph rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98, the 35 U.S.C. §102(b) rejection of claims 59, 60, 75, and 98, the 35 U.S.C. §102(b) rejection of claims 59, 60, 64, 65, 75, 77, 78 and 98, and the 35 U.S.C. §103(a) rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98.

1. **35 U.S.C. §112, first Paragraph, written description rejection of claims 59, 60, 64, 75, 77 and 98**

Claims 59, 60, 64, 75, 77 and 98 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter, which is not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to pending claims 59, 60, 64, 75, 77 and 98, the Office Action argues that use of the term "AP endonuclease inhibitors" as recited in claim 59, 64, and 77 does not suffice to meet the written description requirement under 35 U.S.C. §112, first paragraph.

As discussed above, claim 59 has been amended to recited that that the AP endonuclease inhibitor includes an amine group and binds to the AP site to prevent AP endonuclease-mediated cleavage of phosphodiester bonds.

Applicants respectfully traverse this rejection as applied to the amended claims because (1) the specification of the application clearly allows persons of ordinary skill in the art to recognize that Applicants were in possession of "AP endonuclease inhibitors" as recited in claims 59, 64, and 77, and (2) the Office Action failed to establish a prima facie case that the specification does not satisfy the written description requirement.

Referring to MPEP 2163.02,

> "The fundamental factual inquiry [for determining compliance with the written description requirement] is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual

> reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)."

The specification of the present application describes AP endonuclease inhibitors by specific examples, formulas, and characteristics such that one skilled in the art would recognize that Applicants had possession of the claimed invention.

> Page 18, lines 18+ notes that AP endonuclease inhibitors include:
>
> "Methoxyamine (MX), N-ethylmaleimide, O^6-benzylguanine, and compounds having structures of formula I: wherein X is O or NH, Y is O, S, or NH, Z is absent or represents O, S, or NH, and R represents a hydrogen or a hydrocarbon moiety, and pharmaceutically acceptable salts thereof."

Page 18, lines 29+ further describes the structure and functional characteristics of other compounds and AP endonuclease inhibitors.

> "In single-nucleotide BER, the deoxyribose phosphate (dRP) in the abasic site is removed by the lyase activity of DNA pol β. Compounds such as methoxyamine react with the aldehyde of an abasic site, making it refractory to the β-elimination step of the dRP lyase mechanism, thus blocking single-nucleotide BER."

In other words, compounds such as methoxyamine that include an amine group can react with an aldehyde group to form an imine or Schiff base reaction product and this imine or Schiff base reaction product is refractory to the β-elimination step of the dRP lyase mechanism, thus blocking single-nucleotide BER.

Page 19, lines 1+ further notes other compounds, all of which include amine groups, can react with the aldehyde groups of the AP sites:

> "Suitable AP endonuclease inhibitors may act by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds, or by acting directly on AP endonuclease. Other compounds that may possess AP endonuclease inhibitory activity (e.g., by binding to AP sites and preventing APE-mediated cleavage of phosphodiester bonds) include Other potential inhibitors include O-benzylohydroxylamine; ethyl aminooxyacetate; aminooxyacetic acid; ethyl aminooxyacetate; $H_2NOCHMeCO_2H$; carboxymethoxyamine; aminooxyacetic acid; $HN=C(NH_2)SCH_2CH_2ONH_2$; $H_2NO(CH_2)_3SC(NH_2)=NH$; $MeOC(O)CH(NH_2)CH_2ONH_2$;$H_2NOCH_2CH(NH_2)CO_2H$; canaline; $H_2NO(CH_2)_4ONH_2$; O-(p-nitrobenzyl)hydroxylamine; 2-amino-4-(aminooxymethyl)thiazole; 4-(aminooxymethyl)thiazole; O,O'-(o-phenylenedimethylene)dihydroxylamine; 2,4-dinitrophenoxyamine; O,O'-(m-phenylenedimethylene)dihydroxylamine; O,O'-(p-phenylenedimethylene)dihydroxylamine; $H_2C=CHCH_2ONH_2$; $H_2NO(CH_2)_4ONH_2$; $H_3C\text{--}(CH_2)_{15}\text{--}O\text{--}NH_2$, 2,2'-(1,2-ethanediyl)bis(3-aminooxy)butenedioic acid dimethyl diethyl ester; compounds having any of the following structures: and pharmaceutically acceptable salts of any of these compounds."

Additionally, the specification also discloses a method of identifying additional AP endonuclease inhibitors for use in the present invention. The specification describes a high throughput screening assay to identify new inhibitors of BER which have the ability to block AP site cleavage.

Page 37, line 31 to page 39, line 71 (and Fig. 23A and 23B) state:

> "High-throughput screening methods include two molecular reaction assays:
> 1. Analysis of chemical--modified AP Sites assayed by Aldehyde Reactive Probe (ARP). This is a competitive assay to measure the reactivity with AP site between ARP reagent (Dojindo Molecular Technologies Inc., Gaithersburg, Md.) and the screening compounds. ARP and MX have a similar reactivity with AP sites. They react specifically with an aldehyde group that is open ring form of the AP sites. Thus this assay will allow identification of compounds with potential to block AP site repair based on the binding affinity and

efficiency to AP sites of screening compounds compared to ARP and MX.

a. AP site standard preparation: AP sites were produced in a calf thymus DNA by heat/acid-buffer solution. Intact calf thymus DNA was added to sodium citrate buffer (10 mM sodium citrate containing 10 mM NaH_2PO_4 and 10 mM NaCl, pH 5.0) and held at 70 °C. for 30 min. The reaction was stopped by chilling rapidly on ice, and the DNA was then precipitated with cold ethanol, washed with 70% ethanol, dried, and resuspended in sterilized distilled water.

b. AP-DNA (15 pg) was incubated with test compounds at different concentrations at 37 °C. for 30 min prior to ARP (1 mM) or ARP alone (Dojindo Molecular Technologies Inc., Gaithersburg, Md.) for 30 min. After precipitation and wash with ethanol, DNA was resuspended in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.2). DNA was heat-denatured at 100.degree. C. for 5 min, quickly chilled on ice, and mixed with an equal amount of 2 M ammonium acetate. The single-stranded DNA was then immobilized on a BAS-85 NC membrane (Schleicher and Schuell) using a vacuum filter device (Schleicher and Schuell). The NC membrane was incubated with streptavidinconjugated horseradish peroxidase (BioGenix) at room temperature for 30 min. After NC membrane was rinsed with washing buffer containing NaCl (0.26 M), EDTA (1 mM), Tris-HCl (20 mM), and Tween 20 (1%), ARP-AP sites are visualized with ECL reagents (Amersham Corp.) (FIG. 22A) and quantitated by scanning densitometer (FIG. 22B).

2. AP sites cleavaged by AP-endonuclease (APE). This assay confirms that AP sites modified by potential BER inhibitors are resistant to cleavage by APE, (Trevigen, Gaithersburg, Md.) a BER protein. The assay may be performed as follows (see also FIGS. 23A and B):

a. AP site is prepared by replacing single nucleoside with deoxyuridine in duplex oligonucleotides (40 mer).

b. Regular AP site is produced in the duplex oligonucleotides by human uracil DNA glycosylase (LIDGase, Trevigen, Gaithersburg, Md.) to remove the uracil residue.

c. To generate MX-adducted AP site substrates: the UDG-treated duplex oligonucleotides are mixed with 10 mM MX in buffer containing 10 mM KPO4, pH 7.1 and incubated at 37 °C. After 30 min, the substrates are recovered by ethanol precipitation, lyophilized, resuspended in water, and stored at -20 °C.

d. APE-cleavage reaction: DNA substrates containing either regular AP-sites or chemicalmodified AP sites are incubated with APE (Trevigen, Gaithersburg, Md.) for 30 min and reactants are precipitated with 100% cold ethanol, washed with 70% ethanol and resuspended in TE buffer. The reactants are resolved by denaturing 20% polyacrylamide gel electrophoresis and visualized by silver staining (Silver Staining Kit, Pharmacia Biotech)."

Thus, not only does the specification disclose specific AP endonuclease inhibitors, distinguishing characteristics to identify the AP endonuclease inhibitors, and an assay to identify new AP endonuclease inhibitors of BER, the specification identifies a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage).

The Federal Circuit has stated that the written description requirement does not require the applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989) (citations omitted). The disclosure of a class compounds as well as distinguishing identifying characteristics is sufficient to show that the Applicants were in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

The specification of the present application clearly allows one skilled in the art to recognize what is claimed based on the disclosure of the characteristics of AP endonuclease inhibitors, the disclosure of a vast number of AP endonuclease inhibitors, as well as means to identify additional AP endonuclease inhibitors. Therefore, in view of the foregoing Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, that they were in possession of the invention, and that the invention, in that context, is claimed.

Additionally, regardless of the sufficiency of the disclosure in the specification, the Office Action has failed to establish a prima facie case that the specification does not satisfy the written description requirement. The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The Office Action has failed to provide any evidence in fact or reasoning that the specification fails to meet the written description requirement. The Office Action has merely cited a Federal Circuit decision without correlating the decision with the specific disclosure in the present application.

The Office Action cites Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004) stating:

> "that the ability to find compounds based on a functional property, even when the method of determining the same is clearly disclosed , does not meet the written description requirement."

In *Rochester,* a disputed patent claimed all compounds that could inhibit the cox-2 enzyme without inhibiting the cox-1 enzyme. According to the Rochester

court, it was inappropriate for the patentee to make this claim when it had not identified these compounds structurally but, rather, had only suggested as assay that might be used to identify the compounds.

In the present application, Applicants have provided more than to just suggest an assay, which might be used to identify useful compounds. As discussed above, the Application describes a specific AP endonuclease inhibitor for use in the present invention (e.g., methoxyamine), the general structure of compounds useful as AP endonuclease inhibitors in the present invention, a specific functional characteristic of potential BER inhibitors (blocking AP site cleavage), and an assay to identify new BER inhibitors.

Since the specification adequately discloses a combination of identifying characteristics that distinguish the claimed invention from other materials, it would lead one of skill in the art to the conclusion that Applicants were in possession of the claimed species.

Moreover, the Office Action has provided no evidence to doubt veracity of the statements made in the specification or to show in any manner that the subject matter recited in the application and claims is unpredictable. It is well established that a general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description. MPEP 2163.04. Accordingly, Applicants respectfully request that the 112 first paragraph written description rejection of claims 59, 64 and 77 be withdrawn because the specification of the application clearly allows persons of ordinary skill in the art to recognize Applicants were in possession of "AP endonuclease inhibitors" as recited in claim 59,

64, and 77, and the Office Action failed to established a prima facie case that the specification does not satisfy the written description requirement.

2. 35 U.S.C. §112, first paragraph, enablement rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98

Claims 59, 60, 64, 65, 75, 77, 78, and 98 are rejected under 35 U.S.C. 112, first paragraph, for failure to comply with the enablement requirement.

The Office Action argues that to practice the present invention as claimed in the current application, a person of ordinary skill in the art would have to engage in undue experimentation. The Office Action specifically argues that the specification does not reasonably provide enablement for treating the broader method of potentiating a therapeutic effect of anticancer agents, which induce formation of AP sites.

Applicants traverse the foregoing rejection as applied to the currently amended claims and submit that the amount of direction or guidance disclosed in the specification is sufficient to enable the skilled artisan to make and use the claimed methods using only routine experimentation.

With respect to amended claim 59, Applicants have disclosed in the instant specification known anticancer agents and the use of such agents to induce formation of AP sites as recited in claim 59. Specifically, the specification recites at page 22, lines 19+, that:

> "Anticancer agents that induce the formation of AP sites include intercalating agents such as bleomycin, adriamycin, quinacrine, echinomycin (a quinoxaline antibiotic), and anthrapyrazoles.
>
> Radiation, such as gamma radiation, UVA, and UVB, can be used to generate AP sites according to the methods of the invention. Ultraviolet

light is absorbed in DNA with the formation of UV-specific di-pyrimidine photoproducts. Exposure to gamma irradiation, UVA, and UVB can induce damaged pyrimidine photodimers.

Anticancer agents that induce the formation of AP sites include DNA oxidizing agents such as hydrogen peroxide.

Anticancer agents that induce the formation of AP sites include alkylating agents such as temozolomide (TMZ), 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), $MeOSO_2(CH_2)_2$-lexitropsin (Me-Lex), cis-diamminedichloroplatinum II (cisplat; cis-DDP), mitomycin bioreductive alkylating agents, quinones, streptozotocin, cyclophosphamide, nitrogen mustard family members such as chloroambucil, pentostatin (and related purine analogs), fludarabine, bendamustine hydrochloride, chloroethylating nitrosoureas (e.g., lomustine, fotemustine, cystemustine), dacarbazine (DTIC), and procarbazine. In certain embodiments, the alkylating agent is a nitrosoruea such as a mustine, i.e., a compound having a structure of Formula II, wherein R is an optionally substituted hydrocarbon substituent, such as an alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, aralkyl, or a heteroaralkyl: In preferred embodiments, R is a substituent shown below or to the right of Formula I, i.e., the chemotherapeutic is carmustine (BCNU), chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, or semustine. In certain related embodiments, the chloroethyl group of Formula I is replaced by a methyl group, as in streptozocin. In certain embodiments, however, R is not 2-chloroethyl, i.e., the compound is not BCNU.

Alkylating agents can function by adding methyl groups to DNA, cross-linking macromolecules essential for cell division, and linking guanine bases in DNA through their N_7 atoms. Both inter- and intra-strand cross-links can be mediated by alkylating agents. Inter-strand cross-links prevent the separation of the DNA strands necessary for cell division, and by being more difficult to repair, constitute the more lethal lesion.

In certain embodiments, the anticancer agent is selected from radiosensitizers such as 5-iodo-2'-deoxyuridine (IUdR), 5-fluorouracil (5-FU), 6-thioguanine, hypoxanthine, uracil, ecteinascidin-743, and camptothecin and analogs thereof.

In certain embodiments, the anticancer agent is not temozolomide. In certain embodiments, the anticancer agent is not BCNU. In certain embodiments, the anticancer agent is not PE128723, 6-AN, 3-AB, BCNU, or temozolomide."

These known anticancer agents can be used to treat various cancers. The specific cancers treated by each of these anticancer agents are well known to one skilled in the art. For example, Williams and Lemke, *Foye's Principals of Medicinal Chemistry.*, 5th ed. Baltimore: Lippincott, Williams, & Wilkins, 2002, 928-945 indicate, which cancers these anticancer agent are currently used or approved for treating. Other sources, such as the Nation Cancer Institute, as well as the FDA indicate specific cancers that these anticancer agents can be used for treating.

Applicants have discovered that these anticancer agents (as well as other anticancer agents) can function at least in part by forming AP sites of DNA of the specific cancer cells the agents are administered to treat. Specifically, the present application states at page 17 that:

> "Injury to DNA is minimized by enzymes that recognize errors, remove them, and replace the damaged DNA with corrected nucleotides. DNA damage occurs when a single-strand break is introduced, a base is removed leaving its former partner unpaired, a base is covalently modified, a base is converted into another that is not appropriately paired with the partner base, or a covalent link is introduced between bases on opposite strands. Excision repair systems remove the mispaired or damaged base from the DNA strand and then synthesize new DNA to replace it. Base excision repair (BER) is initiated during replication of DNA and allows for correction of damaged bases/mispaired bases prior to completion of replication.
>
> Base excision repair is initiated by a DNA glycosylase that removes N-glycosidic (base-sugar) bonds, liberating the damaged base and generating an abasic site (AP site). An apurinic or apyrimidinic site results from the loss of a purine or pyrimidine residue, respectively, from DNA. uracil residues result from the spontaneous deamination of cytosine and can lead to a C-T transition if unrepaired. There is also a glycosylase that recognizes and excises hypoxanthine, the deamination product of adenine. Other glycosylases remove alkylated bases (such as 3-methyladenine, 3-methylguanine, and 7-methylguanine), ring-opened purines, oxidatively damaged bases, and in some organisms, UV photodimers.

> The AP site is further processed by a 5'-3' endonuclease (AP endonuclease (APE)) that incises the phosphodiester bond on both sides of the damaged purine or pyrimidine base. The AP endonucleases introduce chain breaks by cleaving the phosphodiester bonds at the AP sites."

The present application also teaches that the BER inhibitors can potentiate the effect of these cancer agents by inhibiting base excision repair, which is one of the mechanisms the cancer cells use to inhibit the cytotoxic function of the anticancer agents.

Applicants have also provided working examples in the present application to show that BER inhibitors can be used to potentiate the effect of anticancer agents that form AP sites. Specifically, Example 1 of the present application shows that methoxyamine, a BER inhibitor, potentiates the effect of TMZ, an anticancer agent that induces formation of AP sites; Example 4 shows that BER inhibitors potentiate the effect of chlorethylating agents that induce formation of AP sites; Example 10 shows that BER inhibitors potentiate the effect of an oxidizing agent that induces formation of AP sites in cancer cells; and Example 11 shows that BER inhibitors potentiate the effect of radiosensitizing agents.

Thus, the appropriate question for determining whether the enablement requirement has been satisfied in the present case is whether the instant specification teaches the ordinary skilled artisan a method of administering a BER inhibitor in combination with an anticancer agent that induces formation of AP sites for the treatment of cancer. Applicants respectfully submit that one skilled in the art would have been able to perform the foregoing methods based on the specification as well as the examples noted in the specification.

In response to Applicants' argument, the Office Action asserts, in the present Office Action, that U.S. Patent No. 4,325,950 discloses a BER inhibitor, caffeine, while showing increased cell death in cell cultures with cis-$Pt(NH_3)_2Cl_2$ is not reasonably correlated to in vivo testing and that one of ordinary skill in the art would not accept the assertion that there will be a potentiated therapeutic effect, which is reasonably interpreted to include treatment in vivo.

In contrast to the Office Action's assertion and U.S. Patent No. 4,325,950, Terzoudi et al.; Cancer Res. 65: (24) 2005 (a copy of which is attached) teaches caffeine has been shown to be an inhibitor of ATM/AT, which are the key components of DNA damage checkpoint and responsible for cell cycle arrest and any necessary repairs. Thus, it is recognized by skilled artisans that caffeine can inhibit DNA damage induced by anticancer agents.

Moreover, Seo et al.; Cancer Res. 2006: (1) 2006 (a copy of which is attached) teaches that caffeine is a "base analogue" of adenine and, in fact, can be incorporated into a growing DNA instead of adenine. Seo et al. further note that caffeine can sensitize cancer cells to IR radiation and inhibit base excision repair of generated AP sites in DNA. Seo et al. also suggest that the degree of checkpoint abrogation by caffeine correlates with the extent repair inhibition of DNA double strand breaks and consequently cellular radiosensitivity. Thus, Seo et al. recognize that caffeine can potentiate the toxicity of an anticancer agent.

Accordingly, for the reasons of record and in contrast to the Examiner's assertions, the instant specification does enable one skilled in the art to practice the claimed invention and it would not require undue experimentation to practice the

invention as claimed. Moreover, the reference relied upon by the Examiner provides no evidence that the claimed invention could not be successfully practiced. Applicants therefore, requests reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejection of claim 59.

Claims 60, 64, 65, 75, 77, 78, and 98 depend either directly or indirectly from claim 59, therefore Applicants respectfully request that the 35 U.S.C. §112, first paragraph, rejection of claims 60, 64, 65, 75, 77, 78, and 98 also be withdrawn.

3. 35 U.S.C. §102(b) rejection of claims 59, 60, 75, and 98

Claims 59, 60, 75, and 98 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,325,950 to Cramer (hereinafter, "Cramer"). The Office Action argues that Cramer teaches caffeine, an inhibitor of DNA repair, has been shown in cell culture studies to greatly increase cell kill caused by cis-$PT(NH_3)_2Cl_2$.

Claim 59 is not anticipated by Cramer because Cramer does not teach administration to a cancer cell of a patient with cancer an anticancer agent and a BER inhibitor at an amount effective to potentiate the cytotoxicity of the anticancer agent.

Cramer, as discussed above, teach at column 1, lines 22-28, that:

> "Caffeine is an inhibitor of DNA repair and it has been shown in cell culture studies that caffeine greatly increases cell kill caused by cis $Pt(NH_3)_2Cl_2$. While these cell culture studies have been demonstrably successful in vitro, they have not been successfully replicated in vivo, i.e., no enhancement of anti-cancer activity occurs when these compounds are combined."

Cramer therefore teaches administering caffeine in combination with cis $Pt(NH_3)_2Cl_2$ to a patient with cancer but does not teach administering caffeine to the patient at an amount effective to potentiate the cytotoxicity of cis $Pt(NH_3)_2Cl_2$.

Cramer further teaches that a $Pt(caffeine)Cl_3$ complex can be used to treat cancer in a patient. Administration of a $Pt(caffeine)Cl_3$ complex to a patient, however, does not teach administration of an anticancer agent and BER inhibitor as recited in claim 59 because claim 59 recites separate anticancer agent and BER inhibitors are administered to a patient. The Federal Circuit has held it will not "carve out a portion" of one component in to meet separate limitations recited in a claim. *Jenric/Pentron Inc. v. Dillon Co.*, 54 USPQ2d 1086, 1090 (Fed. Cir. 2000). Thus, Cramer does not teach administrating to a patient with cancer an anticancer agent and a BER inhibitor at an amount effective to potentiate the cytotoxicity of the anticancer agent. Therefore, withdrawal of the anticipation rejection of claim 59 is respectfully requested.

Claims 60, 75, and 98 depend directly from claim 59 and are therefore allowable over Cramer because of the aforementioned deficiencies discussed above with respect to the rejection of claim 59 and because of the limitations recited in claims 60, 75, and 98.

4. 35 U.S.C. § 102 rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98

Claims 59, 60, 64, 65, 75, 77, 78, and 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Fortini et al. (Carcinogenesis vol. 13, no. 1 (1992) pp.87-93). The Office Action argues Fortini et al. teach methoxyamine provides protection from the cytoxicity of Sn1 alkylating agents, where such are administered together, and

the potentiating effect would be inherent given the same class of anticancer agents, alkylating agents instantly claimed is administered with the same BER inhibitor, methoxyamine.

Claim 59 is not anticipated by Fortini et al. because Fortini et al. do not teach: (1) administration of an anticancer agent and a BER inhibitor to a cancer cell of a patient with cancer, and (2) administration of an amount of BER inhibitor effective to potentiate the cytotoxicity of the anticancer agent.

Fortini et al. teach administration of methoxyamine in combination with an alkylating agent to CHO cells in vitro. Fortini et al. note on page 87, paragraph 2 that they

> "show in this paper that MX [methoxyamine], by reacting with these AP sites, protects CHO from cytoxicity, mutagenicity and sister chromatid exchanges (SCE) induced by Sn1 type ethylating agents. Furthermore, this protective effect is also extended to methylating agent damage."

A CHO cell is not a cancer cell of a patient with cancer. Moreover, the BER inhibitor as recited in claim 59 is administered at an amount to potentiate cytotoxicity of the anticancer agent not protect the cells from cytotoxicity. Accordingly, Fortini et al. fails to teach all of the limitations of claim 59 and withdrawal of the 35 USC 102(b) rejection in view of Fortini et al. is respectfully requested.

Claims 60, 64, 65, 75, 77, 78, and 98 depend either directly or indirectly from claim 59 and are therefore allowable over Fortini et al. because of the aforementioned deficiencies discussed above with respect to the rejection of claim 59 and because of the limitations recited in claims 60, 64, 65, 75, 77, 78, and 98.

5. 35 U.S.C. § 103(a) rejection of claims 59, 60, 64, 65, 75, 77, 78, and 98

Claims 59, 60, 64, 65, 75, 77, 78, and 98 are rejected under 35 U.S.C. 102(a) as being obvious in view of Fortini et al (Carcinogenesis vol. 13, no. 1 (1992) pp.87-93). The Office Action argues Fortini et al. teach methoxyamine provides protection from the cytoxicity of Sn1 alkylating agents, where such are administered together and the potentiating effect would be inherent given the same class of anticancer agents is administered with the same BER inhibitor, methoxyamine. Moreover, the Office Action argues it would have been obvious that the in vitro results of Fortini et al. would mimic the in vivo results.

Claim 59 is not obvious in view of Fortini et al. because Fortini et al. do not teach administration of an anticancer agent and a BER inhibitor to a cancer cell and Fortini et al. teach away from administering to a patient with cancer an amount of BER inhibitor effective to potentiate the cytotoxicity of an anticancer agent.

As discussed above, Fortini et al. teach administration of methoxyamine in combination with an alkylating agent to CHO cells in vitro. A CHO cell is not a cancer cell of a patient with cancer nor does the Office Action provide any evidence in fact or technical literature that an in vitro CHO assay is recognized by the skilled artisan as being a model for a cancer cell or of treating cancer in vivo. As the Examiner bears the burden of establishing a prima facie case of obviousness, Applicants respectfully request that the Examiner provide support for this assertion in the technical literature or withdrawal this rejection.

Additionally, Fortini et al. teach away from administering to a patient with cancer a BER inhibitor at an amount to potentiate the cytotoxicity of the anticancer agent. Fortini et al. note on page 87, paragraph 2 that they

> "show in this paper that MX [methoxyamine], by reacting with these AP sites, protects CHO from cytoxicity, mutagenicity and sister chromatid exchanges (SCE) induced by Sn1 type ethylating agents. Furthermore, this protective effect is also extended to methylating agent damage."

Thus, Fortini et al. teach methoxyamine protects CHO cells from the cytotoxic effects of anticancer agents and teach away from administering to a patient with cancer an amount of BER inhibitor effective to potentiate the cytotoxicity of a anticancer agent. Therefore, withdrawal of the 35 USC 103(a) rejection in view of Fortini et al. is respectfully requested.

Claims 60, 64, 65, 75, 77, 78, and 98 depend either directly or indirectly from claim 59 and are therefore allowable over Fortini et al. because of the aforementioned deficiencies discussed above with respect to the rejection of claim 59 and because of the limitations recited in claims 60, 64, 65, 75, 77, 78, and 98.

In view of the foregoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above-identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

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